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Case-cohort study of plasma phospholipid fatty acid profiles, cognitive function, and risk of dementia: a secondary analysis in the Ginkgo Evaluation of Memory Study

Manja Koch,[1] Jeremy D Furtado,[1] Steven T DeKosky,[2] Annette L Fitzpatrick,[3] Oscar L Lopez,[4] Lewis H Kuller,[5] Kenneth J Mukamal,[6] and Majken K Jensen[1,7]

[1]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA; [2]Department of Neurology, University of Florida, Gainesville, FL, USA; [3]Departments of Family Medicine, Epidemiology, and Global Health, University of Washington, Seattle, WA, USA; [4]Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [5]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA; [6]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; and [7]Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Background: Phospholipids are biomarkers of dietary fat intake and metabolism, linked to several cardiometabolic disorders. Few prospective studies have assessed plasma phospholipids in relation to dementia risk and cognitive function.

Objectives: We aimed to evaluate the association between a decrease in linoleic acid accompanied with an increase in other fatty acids and cognitive function and dementia risk.

Methods: We conducted a case-cohort study nested within the Ginkgo Evaluation of Memory Study. We included 1252 participants, 498 of whom who developed dementia during a mean of 5 y of follow-up. We measured 45 individual plasma phospholipids (as a percentage of total plasma phospholipid fatty acids) by GC and related these to Modified Mini-Mental State Examination (3MSE) scores at baseline and neurologist-adjudicated incidence of all-cause dementia and Alzheimer disease (AD), adjusting for sociodemographic and clinical characteristics.

Results: Substitution of 1% of SFAs for 1% of linoleic acid, the predominant polyunsaturated n–6 (ω-6) fatty acid, was associated with higher risk of dementia (HR per 1% of SFAs instead of linoleic acid = 1.03; 95% CI: 1.00, 1.07) and a 0.08 point lower 3MSE score at baseline (95% CI: −0.12, −0.03), signifying worse cognitive function. When compared with linoleic acid, we found no associations of total monounsaturated, n–3 polyunsaturated, or *trans* fatty acids with risk of dementia or AD. However, the substitution of 1% of the marine n–3 PUFA DHA for linoleic acid was associated with lower risk of dementia (HR = 0.86 per 1% of DHA instead of linoleic acid; 95% CI: 0.76, 0.96). These associations were not modified by apolipoprotein E genotype, mild cognitive impairment at baseline, age, or sex.

Conclusions: Specific elements of diet may be associated with late-life dementia, a hypothesis that requires formal testing in randomized controlled trials and that represents a possible preventive intervention. *Am J Clin Nutr* 2021;114:154–162.

Keywords: Alzheimer disease, fatty acids, cognition, dementia, epidemiology

Introduction

Alzheimer disease (AD) and other dementias are one of the major causes of disability, dependency, and mortality among older individuals in the United States (1). With an increase in

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Supplemental Figure 1 and Supplemental Tables 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to MK (e-mail: mkoch@hsph.harvard.edu).

Abbreviations used: AD, Alzheimer disease; ADAS-cog, Alzheimer Disease Assessment Scale; CDR, Clinical Dementia Rating; CES-D, Center for Epidemiologic Studies–Depression; EVA, Etude du Vieilllisement Artériel; GEMS, Ginkgo Evaluation of Memory Study; MCI, mild cognitive impairment; USLAM, Uppsala Longitudinal Study of Adult Men; 3MSE, Modified Mini-Mental State Examination.

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life expectancy, the prevalence of dementia is rising dramatically, particularly in low- and middle- income countries (2). Given the high disease burden and the lack of disease-modifying treatments, the identification of modifiable risk factors is a major mission in the field of dementia research. The pathophysiology of AD and dementia is multifactorial, and lifestyle factors have been identified as promising targets for dementia prevention (3, 4). Nevertheless, the evidence base for diet as a risk factor for dementia has been assessed as limited and conflicting (4, 5).

Despite inconsistency in previous studies, some of the most intriguing work has suggested neuroprotective effects of fatty acids (6–8). Experimental studies have linked intake of dietary fatty acids to B-amyloid deposition, neuron survival, and synaptic response (9–11). Epidemiological studies, mainly studies of larger sample size and prospective design, have inconsistently found that higher intakes of MUFAs and PUFAs found in plant-based liquid oils and lower intakes of *trans* fatty acids found in fried food and SFAs found in meat and dairy products relate to lower risk of dementia and cognitive decline (12–14). Of note, the latter studies have mainly relied on self-reported dietary intake, which is prone to measurement error (13, 15, 16).

Studies with plasma measures of fatty acids found DHA, plentiful in oily fish, to be related to a lower risk of dementia, but few prospective studies exist (17, 18). The relative risk of dementia per increment of 1 SD in DHA concentration was 0.80 (95% CI: 0.65, 1.00) among participants of the Framingham Heart Study and 0.76 (95% CI: 0.59, 0.99) among participants of the Bordeaux sample of the Three-City Study. Furthermore, only a few studies have investigated comprehensive fatty acid panels in the circulation (19), enabling the analysis of multiple fatty acids together. For example, substituting 5% of energy from linoleic acid (18:2n–6), the predominant polyunsaturated n–6 fatty acid in the Western diet, for 5% of energy from SFAs was associated with a 9% lower risk of coronary artery disease (CAD) (20); CAD itself is a risk factor for dementia (21). To address this gap, we examined the association of objectively measured fatty acid profiles from blood with risk of dementia, AD, and cognitive function in a large, community-dwelling population of older adults.

Methods

Study population and design

The Ginkgo Evaluation of Memory Study (GEMS) trial (NCT00010803) enrolled 3069 community-dwelling participants aged 72 y and older with normal cognition or mild cognitive impairment (MCI) from 2000 to 2002 to evaluate the effect of Ginkgo biloba for the prevention of dementia (22). This trial showed no protective effect of Ginkgo biloba, but provided an exceptional resource for secondary analyses because of the dedication of resources to neurologist-adjudicated risk of dementia (23, 24). For this analysis, we used a case-cohort design, as described previously (25). From the 3069 GEMS participants, we included a random subcohort of 1000 participants free of dementia at baseline, with an additional 523 participants diagnosed with dementia during follow-up, of whom 166 overlapped (as expected in a case-cohort design). We excluded 105 participants with no available plasma samples, leaving 1252 participants in the final analysis (**Supplemental Figure 1**). Institutional review boards at each of the 5 investigational centers in the United States and the Data Coordinating Center at the University of Washington in Seattle approved the study, and participants and their proxies provided written informed consent.

Biochemical measurements

The nutritional biomarker laboratory at the Harvard TH Chan School of Public Health, blinded to all clinical information of study participants, measured the concentration of 45 plasma fatty acids in the phospholipid fraction of plasma (14 SFAs, 7 MUFAs, 4 polyunsaturated n–3 fatty acids, 7 polyunsaturated n–6 fatty acids, and 10 *trans* fatty acids), as described previously (26). Total plasma lipids were extracted from a 150 μL aliquot of plasma by mixture with 6 mL of hexane with BHT and 4.5 mL of isopropanol, vortexing, and centrifugation. A 4-mL aliquot of the upper organic layer was removed to a second test tube and evaporated to dryness under nitrogen gas. The lipid residue was reconstituted with 150 μL of chloroform and loaded into a conditioned solid-phase silica column (Sep-Pak® Silica 55–105 μm, glass syringe 5 cc–500 mg; Waters). To elute all lipid species other than phospholipids, the column was rinsed with a total of 6 mL of petroleum ether (boiling point 30–60°C)–diethyl ether–glacial acetic acid (82:18:1) in 1-mL aliquots at a flow rate of 0.2 to 1 mL/min. The phospholipid fraction was then eluted from the column with 6 mL of methanol-water (9:1) in 1-mL aliquots collected together in a test tube. This eluent was then evaporated to dryness under nitrogen gas and the sample residue was methylated as described previously (26). Fatty acid methyl esters from the phospholipid fractions were analyzed by GC with flame ionization detection (27). Peak retention times were identified by injecting known standards individually and as a mix, and purity ranges were all >99% (NuCheck Prep). The Agilent Technologies ChemStation A.08.03 software was used for analysis. The CVs were monitored by analyzing control samples (**Supplemental Table 1**).

Dementia diagnosis and cognitive assessment

Incident dementia was ascertained up until 2008 using criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV). At study entry, each participant underwent a detailed neuropsychological battery of 10 tests capturing the cognitive domains construction, memory, language, executive functions, attention/psychomotor speed, and premorbid intellectual functioning. Participants completed the Clinical Dementia Rating (CDR) scale and the Modified Mini-Mental State Examination (3MSE) semi-annually. From 2000 to 2004, trained evaluators administered the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-cog) semi-annually, and annually thereafter (28). Results of the 3 cognitive tests were used to mandate re-administration of the neuropsychological battery when the scores declined by a prespecified cutoff (23).

Participants suspected of potentially having cognitive impairment were referred for neurological and medical evaluation and brain MRI. Following this evaluation, final dementia diagnosis was made by an expert panel using a validated protocol (using criteria from the National Institute of Neurological Disorders

and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences, the National Institute of Neurological and Communication Disorders and Stroke, Alzheimer's Disease and Related Disorders Association, and the Alzheimer's Disease Diagnostic and Treatment Centers) (29–31). The panel categorized participants with dementia as having a subtype of vascular dementia, AD, mixed dementia, or other dementia (32). Based on the criteria from the International Working Group on Mild Cognitive Impairment (33), participants were considered to have MCI if participants scored at or below the 10th percentile for education- and age-adjusted norms on 2 or more of 10 selected neuropsychological tests from each cognitive domain and if participants had a score of 0.5 on the CDR scale (34).

Other covariates

At study entry, trained technicians collected demographic and health characteristics in interviews and measured blood pressure, height, and weight. Ethnicity (ethnicity of Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White) were self-defined based on NIH-specified categories and were evaluated for descriptive purposes (23). Participants brought prescription drugs, prescriptions, and over-the-counter medications to the study visit for entry into the medication database. Participants were screened for depressive symptoms using the Center for Epidemiologic Studies–Depression (CES-D) scale. One missing value on the CES-D was replaced with the population median value of 3.

Statistical analysis

Inverse sampling probability-weighted Cox proportional hazards models with a robust estimate of variance were used to evaluate the association of fatty acids with risk of dementia and AD, with study time as the underlying time axis censoring at the time of death, drop-out, or dementia diagnosis, whichever occurred first. We assigned a weight inversely proportional to the sampling probability (3069/1000) to participants without dementia to account for the oversampling of participants with dementia. We tested the proportional-hazards assumption based on Schoenfeld residuals. Inverse sampling probability-weighted linear regression models were used to assess the association of fatty acids with the 3MSE. Because cognitive testing was discontinued in participants who reached a dementia endpoint during follow-up, we restricted analyses of cognitive scores to baseline values. Covariates, selected a priori as potential confounders, included age, sex, race/ethnicity, clinic site, fasting status, education, weekly number of alcoholic drinks, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, CES-D, treatment assignment from the original trial, and apolipoprotein E (*APOE*) ε4 carrier status.

Fatty acids were expressed as a percentage of total plasma phospholipid fatty acids. We evaluated associations per 1% replacement of major plasma phospholipid fatty acids (contributing $\geq$0.02% of total plasma phospholipid fatty acids measured with CVs $\leq$30%) and all *trans* fatty acids (per 0.1% replacement given their lower concentrations) in substitution models. In these analyses, all phospholipid fatty acids except for linoleic acid were included simultaneously, rendering linoleic acid as the reference group. We tested the potential interactions of *APOE* ε4 carrier status, MCI at baseline, race, baseline age, or sex with major phospholipid fatty acids on dementia risk for all fatty acids related to dementia risk or 3MSE scores in the main analysis by including separate interaction terms.

In sensitivity analyses, we evaluated associations per 1-SD higher relative concentration of all 45 plasma phospholipid fatty acids individually based on the exposure distributions in the random subcohort; these analyses represent the substitution of a single fatty acid by all others. We also assessed the association of different phospholipid fatty acid subclasses based on biological function, as described previously (35). Analyses were performed using STATA 12.1 (StataCorp).

Results

Participant characteristics

Among the 1252 participants, the median (IQR) age was 78 (76–81) y; 584 (46.7%) were female and 498 participants were diagnosed with dementia during a median (IQR) follow-up time of 5.8 (3.7–6.4) y. Subcohort members and participants who developed dementia during follow-up had similar age, educational attainment, and BMI (**Table 1**). MCI at baseline was more than twice as frequent in participants who subsequently developed dementia during follow-up compared with subcohort members. In the subcohort, SFAs comprised a median of 44% (IQR: 41–46%) of the total phospholipid fatty acids, with the greatest contributor being palmitic (16:0; median: 23%) and stearic (18:0; median: 17%; Supplemental Table 1) acids. The median DHA concentration was 3.4% (2.6–4.4%) among subcohort participants, 3.29% (IQR: 2.53–4.38%) among participants with all-cause dementia, and 3.23% (2.50–4.26%) among participants with AD. Out of the 45 fatty acids identified, 21 had between-run CVs of 30% or less, and of the latter, 16 fatty acids had a relative concentration of at least 0.2%.

Major phospholipid fatty acids

When compared with linoleic acid, we found no associations of total MUFAs or n–3 PUFAs with risk of dementia, AD, and cognitive function (**Table 2**). Higher SFAs were associated with higher risk of dementia (HR = 1.03 per 1% of SFAs instead of linoleic acid; 95% CI: 1.00, 1.07) and a 0.08 point lower 3MSE score at baseline (per 1% SFAs instead of linoleic acid; 95% CI: −0.12, −0.03), signifying worse cognitive function. When compared with linoleic acid, higher concentrations of the even-chain fatty acids palmitic and stearic acids were each individually associated with worse cognitive function. The sum of the even-chain SFAs myristic acid (14:0), palmitic acid, and stearic acid was unrelated to the risk of dementia and AD but was inversely associated with 3MSE scores (**Supplemental Table 2**). Among fatty acids reflecting stearoyl-CoA desaturase-1 activity, the ratio of palmitoleic acid (16:1n–7c)to palmitic acid was unrelated to risk of dementia, AD, and cognitive function, but the ratio of oleic acid (18:1n–9c) to stearic acid was inversely related to risk of AD (HR = 0.33 per 1 unit; 95% CI: 0.11, 0.96) (Table 2). Higher DHA was associated with a lower risk

TABLE 1 Baseline characteristics of 1252 participants of the Ginkgo Evaluation of Memory case-cohort study[1]

Characteristics	Participants	
	Random subcohort ($n = 911$)	Dementia cases during follow-up ($n = 498$)
Male sex, *n* (%)	493 (54)	260 (52)
Age, median (IQR), y	78 (76, 81)	79 (77, 82)
Ethnicity, *n* (%)		
Hispanic or Latino	10 (1)	7 (1)
Non-Hispanic and non-Latino	851 (93)	444 (89)
Unknown	50 (5)	47 (9)
Race, *n* (%)		
White	871 (96)	469 (94)
Black or African American	26 (3)	19 (4)
Asian, Native Hawaiian, or Other Pacific Islander	7 (1)	6 (1)
Other	7 (1)	4 (1)
Education, median (IQR), y	14 (12, 16)	14 (12, 16)
Weekly drinks, median (IQR),[2] no.	0.04 (0, 2.7)	0.02 (0, 2.1)
Current smoking,[3] *n* (%)	37 (4)	19 (4)
BMI,[4] kg/m^2	27 (24, 29)	26 (24, 28)
Lipid-lowering medication use, *n* (%)	241 (26)	152 (31)
History, *n* (%)		
Cardiovascular disease	304 (34)	189 (38)
Diabetes	78 (9)	47 (9)
Mild cognitive impairment[5]	150 (16)	193 (39)
Clinical dementia rating,[6] *n* (%)		
0	518 (57)	183 (37)
0.5	391 (43)	314 (63)
1	1 (0.1)	0 (0)
Modified Mini-Mental State score, median (IQR)	94 (90, 97)	91 (87, 95)
Alzheimer Disease Assessment Scale–cognitive score, median (IQR)	6 (5, 8)	8 (6, 10)
Center for Epidemiologic Studies–Depression scale score, median (IQR)	3 (1, 5)	4 (2, 7)
Ginkgo biloba assignment, *n* (%)	454 (50)	264 (53)
Apolipoprotein ε4 allele carrier,[7] *n* (%)	165 (18)	135 (27)
Plasma phospholipid fatty acid, median (IQR),[8] %		
SFAs	44 (41, 46)	44 (41, 46)
MUFAs	11 (10, 12)	11 (10, 12)
PUFAs	42 (40, 44)	42 (40, 44)
trans fatty acids	1.9 (1.5, 2.2)	1.9 (1.6, 2.3)
Dementia during follow-up, *n* (%)	157 (17)	498 (100)
Alzheimer disease	105 (12)	334 (67)
Vascular	9 (1)	23 (5)
Mixed	39 (4)	120 (24)
Other	4 (0.4)	21 (4)

[1]Per the case-cohort study design, the 157 cases that occurred within the random subcohort were included in both the case count and the subcohort count. Percentages are calculated with missing data.

[2]$n = 20$ missing.

[3]$n = 23$ missing.

[4]$n = 7$ missing.

[5]Mild cognitive impairment was diagnosed if participants scored ≤10th percentile for age and education on at least 2 tests of the neuropsychological battery using the Cardiovascular Health Study population as a reference population and while also having a Clinical Dementia Rating global score of 0.5 (34).

[6]$n = 1$ missing.

[7]$n = 267$ missing.

[8]Fatty acids are expressed as a percentage of total plasma phospholipid fatty acids.

of dementia (HR = 0.86 per 1% of DHA instead of linoleic acid; 95% CI: 0.76, 0.96) and AD (HR = 0.80 per 1% of DHA instead of linoleic acid; 95% CI: 0.70, 0.91). In contrast, higher EPA was associated with a higher risk of dementia and AD. The associations of palmitic acid, stearic acid, EPA, and DHA with risk of dementia were not modified by *APOE* genotype, MCI at baseline, race, age at baseline, or sex (all *P* for interaction >0.05). When compared with linoleic acid, all fatty acids were unrelated to ADAS-cog scores (**Supplemental Table 3**).

trans fatty acids

We found no associations of total *trans* fatty acids with risk of dementia, AD, and cognitive function (**Table 3**). Among individual *trans* fatty acids, higher palmitelaidic acid (16:1n–7t)

TABLE 2 HRs for risk of dementia or difference in 3MSE at baseline and 95% CIs per 1% higher concentrations of phospholipid fatty acids and a concomitant 1% lower concentration of linoleic acid at screening visit in 1252 participants of the Ginkgo Evaluation of Memory case-cohort[1]

	HR (95% CI) per 1% replacement		Difference (95% CI) in 3MSE per 1% replacement
	Dementia (n cases = 498)	AD (n cases = 334)	
SFAs[2]	1.03 (1.00, 1.07)	1.03 (0.99, 1.07)	−0.08 (−0.12, −0.03)
Palmitic acid (16:0)[3]	1.03 (1.00, 1.07)	1.03 (0.98, 1.07)	−0.08 (−1.13, −0.03)
Margaric acid (17:0)[3]	0.72 (0.15, 3.43)	0.74 (0.12, 4.47)	0.44 (−1.68, 2.57)
Stearic acid (18:0)[3]	1.03 (0.98, 1.08)	1.03 (0.97, 1.09)	−0.08 (−0.15, −0.01)
Arachic acid (20:0)[3]	0.80 (0.41, 1.56)	0.97 (0.44, 2.12)	0.76 (−0.16, 1.69)
Behenic acid (22:0)[3]	0.15 (0.78, 1.69)	1.17 (0.79, 1.73)	−0.21 (−0.75, 0.34)
MUFAs[3]	1.00 (0.92, 1.08)	0.98 (0.89, 1.07)	0.01 (−0.09, 0.12)
Oleic acid (18:1n–9c)	0.98 (0.88, 1.08)	0.92 (0.82, 1.04)	−0.06 (−0.19, 0.08)
cis-Vaccenic acid (18:1n–7c)	1.35 (0.83, 2.20)	1.44 (0.83, 2.48)	0.73 (0.03, 1.43)
PUFAs			
n–3 fatty acids[3]	0.99 (0.92, 1.06)	0.97 (0.89, 1.06)	−0.03 (−0.12, 0.05)
α-Linolenic acid (18:3n–3c)	0.91 (0.41, 2.01)	0.76 (0.24, 2.41)	0.39 (−1.08, 1.86)
EPA (20:5n–3c)	1.34 (1.07, 1.68)	1.33 (1.03, 1.72)	−0.15 (−0.49, 0.19)
DPA (22:5n–3c)	0.84 (0.48, 1.48)	1.00 (0.52, 1.92)	−0.03 (−0.84, 0.78)
DHA (22:6n–3c)	0.86 (0.76, 0.96)	0.80 (0.70, 0.91)	0.04 (−0.12, 0.20)
n–6 fatty acids			
Linoleic acid (18:2n–6cc)[3]	Reference	Reference	Reference
11c,14c-Eicosadienoic acid (20:2n–6c)[3]	0.98 (0.43, 2.23)	1.16 (0.49, 2.72)	−0.66 (−2.09, 0.77)
Dihomo-γ-linolenic acid (20:3n–6c)[3]	0.99 (0.83, 1.18)	0.85 (0.68, 1.06)	−0.01 (−0.25, 0.22)
Arachidonic acid (20:4n–6c)[3]	0.99 (0.93, 1.05)	0.98 (0.91, 1.05)	0.04 (−0.05, 0.13)
Unknown fatty acids[2]	1.01 (0.70, 1.44)	1.15 (0.76, 1.74)	−0.03 (−0.56, 0.49)
Fatty acid 3[3]	1.06 (0.66, 1.69)	1.22 (0.70, 2.11)	−0.04 (−0.69, 0.62)

[1]HRs were obtained from weighted Cox proportional hazard regression models and differences in the cognitive scores were obtained from weighted linear regression models adjusted for age, sex, race, clinic site, fasting status, education, weekly number of alcoholic drinks, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies–Depression Scale, treatment group assignment, and apolipoprotein E genotype. Fatty acids are expressed as a percentage of total plasma phospholipid fatty acids. AD, Alzheimer disease; DPA, docosapentaenoic acid; 3MSE, Modified Mini-Mental State score.

[2]Replacement for linoleic acid (the sum of SFAs, the sum of MUFAs, the sum of PUFAs except for linoleic acid, the sum of *trans* fatty acids, and the sum of other fatty acids were included simultaneously).

[3]Replacement for linoleic acid (e.g., SFAs 16:0, 17:0, 18:0, 19:0, 20:0, 22:0; the sum of other SFAs; the sum of MUFAs; the sum of PUFAs except for linoleic acid; the sum of *trans* fatty acids; and the sum of other fatty acids were included simultaneously; analog for other individual fatty acids).

instead of linoleic acid was associated with lower risk of dementia and AD (HR for AD = 0.76 per 0.1% of palmitelaidic acid instead of linoleic acid; 95% CI: 0.62, 0.93). Although not statistically significant, higher palmitelaidic acid instead of linoleic acid was associated with a 0.18-point (95% CI: −0.04, 0.40) higher 3MSE score at baseline, signifying better cognitive function. In contrast, replacing linoleic acid with *trans*-vaccenic acid (18:1n–7t) was associated with a −0.23-point (95% CI: −0.36, −0.10) lower 3MSE score at baseline.

Discussion

In this observational study in 1252 older men and women, the replacement of linoleic acid with SFAs, especially palmitic and stearic acid, was associated with higher risk of dementia and worse cognitive function at baseline. Compared with an equivalent relative concentration of linoleic acid, total MUFAs, n–3 PUFAs, or *trans* fatty acids were not associated with risk of dementia, AD, and cognitive function at baseline. However, the substitution of the marine n–3 PUFA DHA for linoleic acid was associated with lower risk of dementia, and substitution of EPA for linoleic acid was associated with higher risk of dementia.

Major phospholipid fatty acids

While several previous epidemiological studies have investigated dietary intake of total saturated, monounsaturated, polyunsaturated, and *trans* fatty acids with dementia risk and cognitive decline (14, 36–38), only a few studies have assessed individual plasma phospholipid fatty acids in relation to dementia outcomes. Higher dietary saturated fat intake has been consistently linked to higher risk of dementia and cognitive decline (14, 36, 38). Other smaller prospective cohort studies have examined associations between plasma SFAs and dementia risk, and findings have conflicted (18, 39, 40). Our findings on a direct association of SFAs with risk of dementia and cognitive function were largely ascribed to palmitic and stearic acid, which are the most abundant SFAs. Similarly, in participants of the Etude du Vieillissement Artériel (EVA) cohort, higher phospholipid stearic acid in erythrocyte membranes, but not total saturated fat or palmitic acid, was related to faster cognitive decline over 4 y of follow-up (39). Each 1-SD increment in stearic acid was associated with a 91% higher likelihood of declining at least 2 points on the Mini-Mental State Examination. In contrast, total saturated fat, as well as palmitic and stearic acid, was unrelated to risk of dementia over a 4-y follow-up in participants of the Bordeaux sample of the Three-City Study (18). In the Uppsala

TABLE 3 HRs for risk of dementia or difference in the 3MSE at baseline and 95% CIs per 0.1% higher concentrations of *trans* phospholipid fatty acids and a concomitant 0.1% lower concentration of linoleic acid at screening visit in 1252 participants of the Ginkgo Evaluation of Memory case-cohort[1]

	HR (95% CI) per 0.1% replacement[2]		Difference (95% CI) in 3MSE per 0.1% replacement[2]
	Dementia	AD	
Sum of *trans* fatty acids	1.02 (0.99, 1.04)	1.01 (0.98, 1.04)	−0.02 (−0.06, 0.02)
Myristelaidic acid (14:1n–5t)	0.99 (0.90, 1.08)	0.95 (0.85, 1.07)	0.12 (−0.01, 0.25)
Palmitelaidic acid (16:1n–7t)	0.84 (0.70, 1.00)	0.76 (0.62, 0.93)	0.18 (−0.04, 0.40)
Petroselaidic acid (18:1n–12t)	1.09 (0.89, 1.33)	1.13 (0.89, 1.43)	0.04 (−0.25, 0.33)
Elaidic acid (18:1n–9t)	1.05 (0.89, 1.24)	1.00 (0.83, 1.22)	0.19 (−0.05, 0.43)
trans-Vaccenic acid (18:1n–7t)	1.05 (0.96, 1.14)	1.05 (0.95, 1.17)	−0.23 (−0.36, -0.10)
trans-Linoelaidic acid			
18:2n–6t	0.83 (0.61, 1.13)	0.74 (0.51, 1.06)	−0.25 (−0.55, 0.05)
18:2n–6ct	1.19 (0.93, 1.53)	1.25 (0.98, 1.59)	0.03 (−0.37, 0.42)
18:2n–6tc	0.83 (0.67, 1.02)	0.79 (0.63, 1.00)	0.06 (−0.25, 0.37)
trans-Gondoic acid	1.02 (0.69, 1.51)	1.10 (0.70, 1.73)	0.21 (−0.35, 0.76)
Rumenic acid (18:2n–7ct)	1.11 (0.95, 1.29)	1.12 (0.94, 1.34)	−0.17 (−0.38, 0.04)

[1]HRs were obtained from weighted Cox proportional hazard regression models and differences in the cognitive scores were obtained from weighted linear regression models adjusted for age, sex, race, clinic site, fasting status, education, weekly number of alcoholic drinks, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies–Depression Scale, treatment group assignment, and apolipoprotein E genotype. Fatty acids are expressed as a percentage of total plasma phospholipid fatty acids. AD, Alzheimer disease; 3MSE, Modified Mini-Mental State score.

[2]Replacement for linoleic acid (individual *trans* fatty acids, the sum of SFAs, the sum of MUFAs, the sum of PUFAs except for linoleic acid, and the sum of other fatty acids were included simultaneously).

Longitudinal Study of Adult Men (USLAM), both 1-SD higher palmitic and stearic acid concentrations assessed in midlife were related to a 28% lower risk of AD after 35 y of follow-up (40). We found stearoyl-CoA-desaturase activity (ratio of 18:1n–9c to 18:0), reflecting the rate-limiting step in the formation of MUFAs from SFAs, to be associated with lower risk of AD. This finding supports further research into the role of de novo lipogenesis and dementia. Consistent with our findings of a lack of an association of total MUFAs and PUFAs with risk of dementia and cognitive function, these fatty acids were also unrelated to cognitive decline in the EVA cohort (39). Conversely, higher total MUFAs and especially palmitoleic acid (16:1n-7c) tended to be associated with a higher risk of dementia in the Three-City Study, and higher concentrations of oleic acid (18:1n-9c) were associated with a nonsignificantly lower risk of dementia in the USLAM cohort. These inconsistencies in findings on SFAs, MUFAs, and PUFAs may be due to differences in follow-up time but may also reflect differences in the biological role of the different blood lipid fractions that were assessed. While our study quantified fatty acids in the phospholipid fraction of plasma, the Three-City Study and USLAM cohort quantified total plasma fatty acids. Phospholipids are the major lipid class in membranes, including plasma membranes of neurons, and thus might be more strongly linked to dementia pathology (41).

In several prospective cohort studies, higher total plasma n–3 PUFAs have been associated with lower risk of dementia and less cognitive decline (18, 39, 42). Conversely, in the Atherosclerosis Risk in Communities Study, the Canadian Study of Healthy Aging, and the present study, total n–3 PUFAs were unrelated to risk of dementia or cognitive decline (43, 44). Importantly, our findings differed by the type of n–3 PUFA. For instance, higher EPA was associated with higher risk of dementia, whereas higher DHA was associated with lower risk of dementia. Similarly, in the Framingham Heart Study, only higher DHA but not EPA was related to lower risk of all-cause dementia (17), and inverse associations with cognitive decline were stronger for DHA than EPA in the EVA cohort (39). These findings are somewhat unexpected given that both n–3 fatty acids originate from fish or seafood sources and both EPA and DHA were inversely related to the risk of dementia in the Three-City Study (18). However, compared with EPA, concentrations of DHA are considerably higher in plasma, and while plasma DHA correlates significantly with DHA in cerebrospinal fluid, plasma and cerebrospinal fluid EPA concentrations do not (45). Furthermore, DHA might be more strongly linked to dementia compared to EPA as the brain is highly enriched in DHA, with 3-fold higher concentrations in the brain compared with other tissues (46). While DHA was even more inversely related to AD, compared with dementia in our study, associations were slightly stronger for dementia than AD in the Framingham Heart Study (17). Some intervention studies on n–3 PUFA supplementation with EPA and DHA failed to prove beneficial effects on cognition (47, 48). However, due to the long induction time of AD, studies with less follow-up time in older populations may not capture the most relevant window of exposure. In support of this hypothesis, a previous randomized, double-blind, placebo-controlled trial in younger individuals, aged 18–45 y, and who consumed diets low in n–3 PUFAs found that DHA supplementation improved episodic memory (6).

Mechanistically, beneficial effects of DHA on brain health are supported by a recent randomized, double-blind, placebo-controlled trial in which daily oral DHA supplementation over 24 mo lowered plasma B-amyloid-42 concentrations, which also points to nutrition in midlife as an important component of later life risk of dementia (8). Further studies on imaging and circulatory biomarkers of Alzheimer's pathology are needed to clarify the role of DHA in disease pathology and if associations differ by dementia subtype.

In our study, higher linoleic acid, the most abundant polyunsaturated n–6 fatty acid in the diet, was associated with a

lower risk of dementia and better cognitive function at baseline compared with substitution by all other fatty acids. Previously, concerns have been raised that linoleic acid, found in vegetable oils, nuts, and seeds, has adverse effects on the brain (49), because of its proinflammatory properties. Linoleic acid can be converted to arachidonic acid and subsequently be metabolized to proinflammatory eicosanoids. However, randomized controlled feeding studies of linoleic acid do not support an increase in inflammatory markers (50). Overall, previous studies on total or individual n–6 PUFAs with dementia risk have been conflicting (18, 40, 43, 51).

trans fatty acids

There is strong evidence that higher intake of *trans* fatty acids increases the risk of type 2 diabetes and cardiovascular disease, 2 important risk factors for dementia (21, 52). Naturally occurring *trans* fatty acids are found in milk and meat from ruminant animals, and artificial *trans* fatty acids are formed in the hydrogenation process of vegetable oils. The US FDA has banned foods with artificial *trans* fatty acids since 2018. As we leveraged samples collected before this ban between 2000 and 2002, the present study offered the unique opportunity to assess the association of *trans* fatty acids with dementia risk and cognitive function (53). In our study, *trans* fatty acids were not uniformly related to dementia risk. Elaidic acid (18:1n–9t) is one of the primary industrially produced *trans* fatty acids that has been linked to higher risk of dementia in the Hisayama study (54). Participants in the highest compared with lowest quartile of elaidic acid concentrations had a 50% higher risk of dementia. In the current study, elaidic acid was unrelated to dementia risk in the substitution analysis for linoleic acid but was related to higher risk of dementia when modeled individually. In our study, higher *trans*-vaccenic acid concentration was associated with worse cognitive function, whereas higher palmitelaidic acid was associated with lower dementia risk, although both *trans* fatty acids are associated with dairy product intake (55).

Our study had some limitations, including the lack of information on dietary intake. With a mean age of 79 y at baseline, the study population was restricted to older individuals. Given an observed increase in cognitive function over the first half of follow-up indicating a learning effect, we limited the analysis of cognitive function to a cross-sectional design. Future studies on prospective associations on plasma fatty acids, cognitive function, and brain pathology would be particularly valuable in middle-aged individuals where pathological changes are likely to occur but dementia incidence is low. Although associations were not modified by race, our analysis was not powered for race-stratified analyses, and population-based studies with greater racial and ethnic diversity are warranted. Similarly, we observed no effect modification by *APOE* ε4 status but did not have large-scale genotyping available to estimate multi-locus genetic risk. Phospholipid fatty acids were assessed as relative concentrations, which inherently accounts for the interrelation of phospholipid fatty acids but does not allow comparison of absolute concentrations to other cohorts. While none of the associations were robust following Bonferroni correction, the hypothesis tests are not independent given that each fatty acid is expressed as the percentage of total fatty acids. The strengths of the present study include the large sample size, prospective design of the dementia analysis, and the assessment of the most comprehensive number of objectively measured individual fatty acids with incident dementia to date. Furthermore, we accounted for a variety of potential confounders in the analyses, including confounding by different fatty acids by using replacement models.

Conclusions

In conclusion, this prospective study provided evidence that substitution of SFAs for linoleic acid was associated with higher risk of dementia and worse cognitive function. Furthermore, the substitution of the marine n–3 fatty acid DHA for linoleic acid was associated with lower risk of dementia. These results suggest that blood concentrations of specific phospholipid fatty acids, which reflect both dietary intake and metabolic influences, could be associated with later-life dementia, a hypothesis that requires formal testing in long-term randomized controlled trials.

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The authors' responsibilities were as follows—KJM and MKJ: designed the research; MK: analyzed the data and drafted the manuscript; and all authors: conducted the research and read, revised, and approved the final manuscript. None of the authors reported a conflict of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application at the Collaborative Health Studies Coordinating Center (https://www.uwchscc.org/), which is part of the Department of Biostatistics in the School of Public Health at the University of Washington.

References

1. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. Alzheimers Dement 2017;13(4):325–73.
2. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. N Engl J Med 2016;374(6):523–32.
3. Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Munoz Sanchez JL, Anstey KJ, Brayne C, Dartigues JF, Engedal K, Kivipelto M, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr Psychiatry 2015;30(3):234–46.
4. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 2015;11(6):718–26.
5. Gustafson DR, Clare Morris M, Scarmeas N, Shah RC, Sijben J, Yaffe K, Zhu X. New perspectives on Alzheimer's disease and nutrition. J Alzheimers Dis 2015;46(4):1111–27.
6. Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, Kennedy D. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. Am J Clin Nutr 2013;97(5):1134–43.
7. Kulzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A, Floel A. Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. J Alzheimers Dis 2016;51(3):713–25.
8. Zhang YP, Lou Y, Hu J, Miao R, Ma F. DHA supplementation improves cognitive function via enhancing Abeta-mediated autophagy in Chinese elderly with mild cognitive impairment: a randomised placebo-controlled trial. J Neurol Neurosurg Psychiatry 2018;89(4):382–8.
9. Pellmar TC. Fatty acids modulate excitability in guinea-pig hippocampal slices. Neuroscience 1991;45(2):273–80.

10. Hosono T, Nishitsuji K, Nakamura T, Jung CG, Kontani M, Tokuda H, Kawashima H, Kiso Y, Suzuki T, Michikawa M. Arachidonic acid diet attenuates brain Abeta deposition in Tg2576 mice. Brain Res 2015;1613:92–9.
11. Oksman M, Iivonen H, Hogyes E, Amtul Z, Penke B, Leenders I, Broersen L, Lutjohann D, Hartmann T, Tanila H. Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. Neurobiol Dis 2006;23(3):563–72.
12. Barnard ND, Bunner AE, Agarwal U. Saturated and trans fats and dementia: a systematic review. Neurobiol Aging 2014;35(Suppl 2):S65–73.
13. Okereke OI, Rosner BA, Kim DH, Kang JH, Cook NR, Manson JE, Buring JE, Willett WC, Grodstein F. Dietary fat types and 4-year cognitive change in community-dwelling older women. Ann Neurol 2012;72(1):124–34.
14. Devore EE, Grodstein F, van Rooij FJ, Hofman A, Rosner B, Stampfer MJ, Witteman JC, Breteler MM. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. Am J Clin Nutr 2009;90(1):170–6.
15. Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, Morris MC. Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. Neurology 2014;83(16): 1410–6.
16. Morris MC. Nutrition and risk of dementia: overview and methodological issues. Ann NY Acad Sci 2016;1367(1):31–7.
17. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol 2006;63(11):1545–50.
18. Samieri C, Feart C, Letenneur L, Dartigues JF, Peres K, Auriacombe S, Peuchant E, Delcourt C, Barberger-Gateau P. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. Am J Clin Nutr 2008;88(3):714–21.
19. Iuliano L, Pacelli A, Ciacciarelli M, Zerbinati C, Fagioli S, Piras F, Orfei MD, Bossu P, Pazzelli F, Serviddio G, et al. Plasma fatty acid lipidomics in amnestic mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis 2013;36(3):545–53.
20. Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, Willett WC, Hu FB. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. Circulation 2014;130(18):1568–78.
21. Wolters FJ, Segufa RA, Darweesh SKL, Bos D, Ikram MA, Sabayan B, Hofman A, Sedaghat S. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. Alzheimers Dement 2018;14(11):1493–504.
22. DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, Burke G, Fried L, Kuller LH, Robbins J, et al. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. Contemp Clin Trials 2006;27(3):238–53.
23. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008;300(19):2253–62.
24. Kuller LH, Ives DG, Fitzpatrick AL, Carlson MC, Mercado C, Lopez OL, Burke GL, Furberg CD, DeKosky ST; Ginkgo Evaluation of Memory Study Investigators. Does Ginkgo biloba reduce the risk of cardiovascular events? Circ Cardiovasc Qual Outcomes 2010;3(1):41–7.
25. Koch M, Aroner S, Mukamal K, Budoff M, McClelland R, Jensen M. HDL subspecies according to apoC-III and non-alcoholic fatty liver disease: the Multi-Ethnic Study of Atherosclerosis. Gesundheitswesen 2017;79(08/09):656–804.
26. Furtado JD, Beqari J, Campos H. Comparison of the utility of total plasma fatty acids versus those in cholesteryl ester, phospholipid, and triglyceride as biomarkers of fatty acid intake. Nutrients 2019;11(9):2081.
27. Baylin A, Kim MK, Donovan-Palmer A, Siles X, Dougherty L, Tocco P, Campos H. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. Am J Epidemiol 2005;162(4):373–81.
28. Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez OL, Dunn LO, Sink KM, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA 2009;302(24):2663–70.
29. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34(7):939–44.
30. American Psychiatric Association. The diagnostic and statistical manual of mental disorders. 4th ed. Arlington (VA): American Psychiatric Association; 1994.
31. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42(3 Pt 1):473–80.
32. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008;300(19):2253–62.
33. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256(3):240–6.
34. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. Neuroepidemiology 2003;22(1):1–12.
35. Forouhi NG, Koulman A, Sharp SJ, Imamura F, Kroger J, Schulze MB, Crowe FL, Huerta JM, Guevara M, Beulens JW, et al. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. Lancet Diabetes Endocrinol 2014;2(10):810–8.
36. Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology 2004;62(9):1573–9.
37. Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM. Diet and risk of dementia: does fat matter? The Rotterdam study. Neurology 2002;59(12):1915–21.
38. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60(7):940–6.
39. Heude B, Ducimetiere P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes—the EVA study. Am J Clin Nutr 2003;77(4):803–8.
40. Ronnemaa E, Zethelius B, Vessby B, Lannfelt L, Byberg L, Kilander L. Serum fatty-acid composition and the risk of Alzheimer's disease: a longitudinal population-based study. Eur J Clin Nutr 2012;66(8):885–90.
41. Yehuda S, Rabinovitz S, Mostofsky DI. Essential fatty acids are mediators of brain biochemistry and cognitive functions. J Neurosci Res 1999;56(6):565–70.
42. Dullemeijer C, Durga J, Brouwer IA, van de Rest O, Kok FJ, Brummer RJ, van Boxtel MP, Verhoef P. n–3 Fatty acid proportions in plasma and cognitive performance in older adults. Am J Clin Nutr 2007;86(5):1479–85.
43. Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 2007;85(4):1103–11.
44. Kroger E, Verreault R, Carmichael PH, Lindsay J, Julien P, Dewailly E, Ayotte P, Laurin D. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. Am J Clin Nutr 2009;90(1):184–92.
45. Jumpertz R, Guijarro A, Pratley RE, Mason CC, Piomelli D, Krakoff J. Associations of fatty acids in cerebrospinal fluid with peripheral glucose concentrations and energy metabolism. PLoS One 2012;7(7):e41503.
46. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. Am J Clin Nutr 2006;83(6 Suppl):1467S–76S.
47. Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS; Age-Related Eye Disease Study 2 Research Group. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on

cognitive function: the AREDS2 randomized clinical trial. JAMA 2015;314(8):791–801.
48. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cufi MN, Dantoine T, Dartigues JF, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol 2017;16(5):377–89.
49. Taha AY. Linoleic acid-good or bad for the brain? NPJ Sci Food 2020;4:1.
50. Johnson GH, Fritsche K. Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials. J Acad Nutr Diet 2012;112(7): 1029.
51. Ruan Y, Tang J, Guo X, Li K, Li D. Dietary fat intake and risk of Alzheimer's disease and dementia: a meta-analysis of cohort studies. Curr Alzheimer Res 2018;15(9):869–76.
52. Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care 2015;39(2):dc151588.
53. Vesper HW, Caudill SP, Kuiper HC, Yang Q, Ahluwalia N, Lacher DA, Pirkle JL. Plasma trans-fatty acid concentrations in fasting adults declined from NHANES 1999–2000 to 2009–2010. Am J Clin Nutr 2017;105(5):1063–9.
54. Honda T, Ohara T, Shinohara M, Hata J, Toh R, Yoshida D, Shibata M, Ishida T, Hirakawa Y, Irino Y, et al. Serum elaidic acid concentration and risk of dementia: the Hisayama Study. Neurology 2019;93(22):e2053–64.
55. Micha R, King IB, Lemaitre RN, Rimm EB, Sacks F, Song X, Siscovick DS, Mozaffarian D. Food sources of individual plasma phospholipid trans fatty acid isomers: the Cardiovascular Health Study. Am J Clin Nutr 2010;91(4):883–93.